ICF for patients with unknown BRCA status to undergo central BRCA testing during, or prior to, neoadjuvant/adjuvant chemotherapy

**Neoadjuvant chemotherapy**
Minimum 6 cycles (containing anthracyclines, taxanes or the combination of both)

**Surgery**
For TNBC: Axillary node positive (≥pN1, any tumour size) If axillary node negative (pN0)
T ≥ 2 cm (≥pT2)
For ER and/or PgR+ HER2−: ≥ 4 positive lymph nodes

**Adjuvant Chemotherapy**
Minimum 6 cycles (containing anthracyclines, taxanes or the combination of both)

**Radiotherapy/additional surgery as required**

**Informed consent for participation in the study for patients with known gBRCA mutation status**

**Randomisation**
(ideally within 8 weeks after last treatment (surgery, chemotherapy or radiotherapy), but in no case longer than 12 weeks)

**Olaparib 300 mg orally twice daily, continuous for 12 months OR**
Placebo orally twice daily, continuous for 12 months

**Mammogram and/or breast MRI 6 months from day 1**

Follow up for local and distant recurrence and survival status
Patients will continue to be followed clinically on a 3 monthly basis during the first 2 years, followed by 6 monthly assessments for the 3rd, 4th and 5th year, and annually thereafter

Yearly breast imaging (mammogram and/or MRI) for 10 years*

*The study will end 10 years after the last patient has been randomised
4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a patient screening log of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

Criteria relevant to Part 1 BRCA screening (Table 1) are marked with (** double asterisk

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. **Provision of informed consent prior to any study specific procedures

2. **Female or male patients must be \( \geq 18 \) years of age

3. a) For patients who underwent initial surgery and received adjuvant chemotherapy
   
   - TNBC patients must have been axillary node-positive (\( \geq pN1 \), any tumour size) or axillary node negative (\( pN0 \)) with invasive primary tumour pathological size \( \geq 2 \) cm (\( \geq pT2 \)).
   
   - ER and/or PgR positive/HER 2 negative patients must have had \( \geq 4 \) pathologically confirmed positive lymph nodes.

b) For patients who underwent neoadjuvant chemotherapy followed by surgery

   - TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR)

   - ER and/or PgR positive/HER2 negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) AND a CPS&EG score \( \geq 3 \). Instructions on how to calculate the CPS&EG score (Mittendorf et al 2011; Jeruss et al 2008) are provided in Appendix I.

4. **Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that is one of the two following phenotypes:

   a) TNBC defined as:

      - ER and PgR negative defined as IHC nuclear staining <1%. All ER and PgR assessments that are locally available must be negative.

      AND
- HER2 negative (not eligible for anti-HER2 therapy) defined as:
  - IHC 0, 1+ without ISH OR
  - IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells OR
  - ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

b) ER and/or PgR positive, HER2 negative breast cancer defined as:

- ER and/or PgR positive defined as IHC nuclear staining ≥ 1%. Any tumour that has been locally assessed as ER and/or PgR positive in either the core biopsy or the surgical specimen is considered to be ER and/or PgR positive. AND

- HER2 negative (not eligible for anti-HER2 therapy) defined as:
  - IHC 0, 1+ without ISH OR
  - IHC 2+ and ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells OR
  - ISH non-amplified with ratio less than 2.0 and if reported, average HER2 copy number < 4 signals/cells (without IHC)

Patients with multifocal or multicentric invasive disease are eligible as long as all the lesions for which HER2 characterization is available are HER2 negative.

Patients with synchronous bilateral invasive disease are eligible as long as all the lesions assessed for HER2 on both sides are negative.

In both cases, the lesion considered at highest risk for recurrence based on the investigator's discretion will be used for eligibility determination.

5. Documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Local g*BRCA* testing results, if available, will be used for establishing eligibility. If local g*BRCA* testing results are not available, central testing will be provided for those patients who otherwise appear to be eligible (see Section 6.2.1).

6. a) Completed adequate breast surgery defined as:

- The inked margins of breast conservation surgery or mastectomy must be histologically free of invasive breast cancer and ductal carcinoma in situ with the exception of the posterior margin if this margin is the pectoralis
major fascia or the anterior margin if this is the dermis. Patients with resection margins positive for lobular carcinoma in situ are eligible.

- Patients with breast conservation must have adjuvant radiotherapy. Patients having mastectomy may have adjuvant radiotherapy according to local policy and/or international guidelines.

b) Completed adequate axilla surgery defined as:

**Adjuvant Chemotherapy Patients:**
- Sentinel lymph node biopsy alone if negative or if lymph node(s) only contain micrometastases (≤2.0 mm) **OR**
- Positive sentinel lymph node biopsy followed by axillary nodal dissection or radiotherapy as per local guidelines **OR**
- Axillary dissection

**Neoadjuvant Chemotherapy Patients:**
- Sentinel lymph node biopsy performed before neoadjuvant chemotherapy:
  - If negative or if lymph node(s) only contain micrometastases (≤2.0 mm), additional axillary surgery is not required
  - If positive, axillary node dissection or axillary nodal radiotherapy should follow completion of neoadjuvant chemotherapy
- Sentinel lymph node biopsy performed after neoadjuvant chemotherapy:
  - If negative, additional axillary surgery not mandated
  - If positive (micrometastases are regarded as positive), additional axillary surgery is required unless the patient is enrolled in an Executive Committee approved, Phase III multicentre clinical trials proposing radiotherapy as alternative treatment of the axilla
- Axillary dissection

7. Completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or the combination of both. Prior platinum as potentially curative treatment for prior cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed. (For neoadjuvant patients all chemotherapy should be delivered prior to surgery. No further cycles of chemotherapy post-surgery are allowed.)
8. Patients must have adequate organ and bone marrow function measured within 28 days prior to randomisation with no blood transfusions (packed red blood cells and/or platelet transfusions) in the past 28 days prior to testing for organ and bone marrow function as defined below:

- Haemoglobin ≥ 10.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10⁹/L
- Platelet count ≥ 100 x 10⁹/L
- Total Bilirubin ≤ ULN (institutional upper limit of normal) except elevated total bilirubin <1.5 x ULN due to Gilbert’s disease or similar syndrome involving slow conjugation of bilirubin
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x ULN
- ALP ≤ 2.5 x ULN

To rule out metastatic breast cancer, patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note PET/CT scan may be used as an alternative imaging techniques).

9. Serum or plasma creatinine ≤ 1.5 x ULN

10. ECOG performance status 0-1

11. a) Women who are not postmenopausal or have not undergone a hysterectomy must have documented negative pregnancy test within 28 days prior to randomisation.

Postmenopausal is defined as one or more of the following:

- Age ≥ 60 yrs
- Age < 60 and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
- Follicle stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range for women under 60
- Radiation-induced oophorectomy with last menses >1 year ago
- Bilateral oophorectomy

b) **Female patients of childbearing potential who are sexually active must agree, with their partners, to the use of two highly effective forms of contraception in
combination throughout the period of taking study treatment and for at least 1 month after the last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse. Male patients must agree, with their partners who are sexually active and of childbearing potential, to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for 3 months after last dose of study drug, or they must totally/truly abstain from any form of sexual intercourse (For details please refer to Appendix F Acceptable Birth Control Methods).

12. **Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations**

13. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour, mandatory*.

*NOTE: For adjuvant patients this refers to the surgical specimen; for neoadjuvant patients, both the pre-treatment biopsy and the surgical specimen with residual disease specimen are requested, but only one is mandatory. If the surgery tumour blocks are available, but cannot be submitted, sites may submit a portion of invasive tumour from the original block, either by taking at least one core of at least 3 mm in diameter, or by splitting the original block in two parts, and re-embedding one in a new block for central submission. If blocks containing pre-neoadjuvant treatment core biopsies are available but cannot be submitted, sections mounted on glass slides prepared from the block can be provided. If tumour sample can't be provided as requested above or if it's not available, approval by Study Team for patient's entry into the trial is required.

14. Patient should be randomised in the trial ideally within a maximum of 8 weeks of completion of their last treatment (surgery, chemotherapy or radiotherapy), but in no case longer than 12 weeks.

### 4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. **Involvement in the planning and/or conduct of the study.**

2. Patients who do not have deleterious or suspected deleterious *gBRCA1* and/or 2 mutations but only have *BRCA1* and/or *BRCA2* mutations that are considered to be non detrimental (e.g., “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favour polymorphism” or “benign polymorphism” etc.).

3. **Previous randomisation in the present study.**

4. **Evidence of metastatic breast cancer.** Patient considered at high risk of having disseminated disease (i.e. those with locally advanced disease, clinical N2-3 or pathological N1-3 with the exception of pN1a in adjuvant patients) should have a CT/MRI scan of the Thorax/Abdomen/Pelvis or any other area as clinically indicated.
and a bone scan or a CT scan with bone windows at any point between diagnosis of the current breast cancer and randomisation to rule out metastatic breast cancer. (Note PET/CT scan may be used as an alternative imaging technique and precludes the need for bone scan). Patients with screening ALT/AST or ALP above institutional upper limit of normal should have liver ultrasound, CT or MRI at any time point between diagnosis of current breast cancer and randomisation. Screening bone scan is required if ALP and/or corrected calcium level are above the institutional upper limit. (Note PET CT scan may be used as an alternative imaging technique).

5. **Exposure to an investigational product within 30 days or five half lives (whichever is the longer) prior to randomisation.

6. **Any previous treatment with a PARP inhibitor, including olaparib and/or known hypersensitivity to any of the excipients of study treatment.

7. **Patients with second primary malignancy, EXCEPTIONS:
   - adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, Ductal Carcinoma in situ (DCIS) of the breast, stage 1 grade 1 endometrial carcinoma
   - other solid tumours and lymphomas (without bone marrow involvement) diagnosed ≥ 5 years prior to randomisation and treated with no evidence of disease recurrence and for whom no more than one line of chemotherapy was applied.

8. Resting ECG with QTc > 470 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec.

9. Patients receiving systemic chemotherapy within 3 weeks prior to randomisation.

10. Patients receiving adjuvant radiotherapy within 2 weeks prior to randomisation.

11. Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further details and the minimum washout period prior to starting olaparib, refer to Appendix I.

12. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 2 peripheral neuropathy.

13. **Patients with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or with features suggestive of MDS/AML.

14. Major surgery within 2 weeks prior to randomisation: patients must have recovered from any effects of any major surgery.
15. Patients considered at poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, extensive bilateral lung disease on High Resolution Computed Tomography scan or any psychiatric disorder that prohibits obtaining informed consent.

16. **Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

17. Pregnant or breastfeeding women.

18. **Patients with known active Hepatitis B or C

19. **Patients known to be HIV positive with one or more of the following:
   a. Baseline CD4 count of < 250 cells/mm³
   b. History of AIDS indicator conditions
   c. Anti-retroviral therapy with any potent CYP3A4 inhibitor (see Section 5.6.2)

20. **Previous allogeneic bone marrow transplant.

21. **Whole blood transfusions in the last 120 days prior to entry to the study which may interfere with gBRCA testing (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no. 8)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.